REMARKS

Claims 1-39 were pending. Claims 1, 3-8, 11-16, 18, 21, 22, 24, 33, 34, and 36-39 have been canceled without prejudice. Applicant reserves the right to pursue the subject matter of the canceled claims in related applications. Claims 2, 9, 10, 17, 19, 20, 23, and 25-32 have been amended to cancel references to non-elected subject matter, to remove dependencies on canceled claims, to correct antecedent basis, and/or to correct certain grammatical errors. Claim 2 has also been amended, and claims 40-42 have been added, to clarify Applicant's invention. Support for the amendment to claim 2 and for new claims 40-42 is found *inter alia* in the specification, for example, as follows: support for complexing "in vitro" is at page 5, lines 15-23; support for new claim 40 is at page 51, lines 20-22, and page 89, lines 3-8; support for new claim 41 is at page 52, lines 4-10; and support for new claim 42 is at page 85, lines 22-25.

1. Claim Objections

The Examiner objected to claims 1-3, 15, 17, 19, 20, 23, 25-33, and 35 for containing subject matter directed to non-elected inventions, *e.g.*, heat shock proteins. In response, Applicant notes that the rejection is moot as it applies to claims 1 and 3, which have been canceled herein. With respect to claim 2, and its dependent claims, Applicant has deleted references to non-elected subject matter from the claims.

2. The Rejections Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn

The Examiner rejected claims 1-3, 15, 17, 19, 20, 23, 25-33, and 35 as allegedly indefinite for the recitation in independent claims 1-3 of the phrase "at least 50% of the different proteins presented [sic, present] in cells." In response, Applicant notes that the rejection is moot as it applies to claims 1 and 3, which have been canceled herein. With respect to claim 2, and its dependent claims, without conceding the correctness of the Examiner's rejection, and in order to further the prosecution of the subject application, the claims have been amended to remove the phrase objected to by the Examiner, rendering this rejection moot.

The Examiner also rejected claim 19 due to insufficient antecedent basis. In response, claim 19 has been amended to correct the antecedent basis.

In view of the above, Applicant submits that the claims satisfy the requirements of 35 U.S.C. § 112, Second Paragraph, and respectfully requests that the Examiner's rejections be withdrawn.

3. The Rejection Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn

The Examiner rejected claims 1-3, 15, 17, 19, 20, 23, 25-33, and 35 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement for methods of preventing cancer. In response, Applicant notes that the rejection is moot as it applies to claims 1 and 3, which have been canceled herein. With respect to claim 2, and its dependent claims, without conceding the correctness of the Examiner's rejection, and in order to further the prosecution of the subject application, Applicant has deleted reference to the prevention of cancer from the claims, rendering this rejection moot.

4. The Rejection Under 35 U.S.C. § 102(e) Should Be Withdrawn

The Examiner rejected claims 1-3, 15, 17, 19, 20, 23, 25-33, and 35 under 35 U.S.C. §102(e) as allegedly anticipated by Li, U.S. Patent No. 6,984,389 ("Li"). In response, Applicant notes that the rejection is moot as it applies to claims 1 and 3, which have been canceled herein. With respect to claim 2, Applicant respectfully submits that claim 2 as amended, and its dependent claims, are novel over Li for the reasons set forth below.

The legal standard for anticipation under 35 U.S.C. § 102 (b) is one of strict identity. A claim is anticipated only if each and every element set forth in the claim is found, either expressly or inherently, in a single prior art reference. *Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631 (Fed. Cir. 1987); *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003); *Atlas Powder Co. v. IRECO, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999). In other words, there must be no difference between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). *See also, Richardson v. Suzuki Motor Co., Ltd.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989)(stating that the "identical invention must be shown in as complete detail as is contained in the patent claim").

Li teaches methods of treating cancer using α2M-peptide complexes. However, the complexes taught by Li are different from the complexes made according to the claims

because the complexes of Li are either (1) endogenously (not *in vitro*) complexed, *i.e.*, the α2M and antigenic peptides are isolated already complexed with each other from antigenic cells or tissues (see *e.g.*, Li at col. 8, lines 15-23); or (2) complexed *in vitro* to specific peptides or proteins selected for their known immunogenicity or antigenicity (*i.e.*, known antigens, see *e.g.*, Li at col. 44-45, sec. 5.4.4), or to specific pools of peptides which have been selected from a protein preparation for their potential immunogenicity or antigenicity, *i.e.*, due to their ability to bind to stress proteins or MHC molecules (see *e.g.*, Li at col. 42, line 45 to col. 43 line 3, sec. 5.4.1, as well as cols. 43-44, sec. 5.4.2 (peptides from stress protein-peptide complexes), and sec. 5.4.3 (peptides from MHC-peptide complexes)).

Li does not anticipate independent claim 2 because Li does not teach each and every element of the claim. Specifically, Li does not teach the *in vitro* made complexes according to claim 2, in which a protein preparation is digested with one or more proteases to produce the antigenic peptides used in the *in vitro* complexing step. The complexes taught by Li are different from the complexes made according to claim 2 because the complexes of Li are either (1) endogenously (not *in vitro*) complexed, *i.e.*, the α2M and antigenic peptides are isolated already complexed with each other from antigenic cells or tissues (see *e.g.*, Li at col. 8, lines 15-23); or (2) complexed *in vitro* but without the protease digestion step of claim 2.

The endogenous complexes of Li, which are isolated from cells or tissues, do not anticipate the complexes of claim 2, which are made *in vitro*, because the *in vitro* made complexes would be expected to comprise different peptides in different amounts than complexes purified from a cell. This is true for several reasons. First, the conditions of complexing are different within a cell versus *in vitro* (*e.g.*, concentration of peptides and α2M, pH, salt concentration, temperature, etc.). These differences will affect both the amount of complexes that form and the particular peptides that comprise the complexes. Second, the pool of peptides available for complexing within a cell will differ from the pool available for complexing according to the *in vitro* methods recited in the claim. One reason for this difference is that proteins and peptides are compartmentalized within a cell, thereby limiting the particular proteins and peptides available for complexing (see *e.g.*, Applicant's specification at p. 10, lines 3-11). In addition, the protease digestion specified in claim 2 produces a population of peptides that does not occur naturally in the cell, and therefore

would not be available for complexing within the cell according to the endogenous method of Li.

The *in vitro* made complexes taught by Li do not anticipate the claimed complexes because the claimed complexes will comprise different peptides in different amounts than the *in vitro* made complexes of Li. This is because the *in vitro* complexing method of Li does not teach protease digestion of proteins as specified in claim 2, which protease digestion produces a population of peptides for complexing that is not present for complexing according to the method of Li. The *in vitro* made complexes taught by Li comprise either a specific peptide or protein (*i.e.*, a known antigen) or pools of peptides or proteins which have been selected for their potential immunogenicity or antigenicity based on their ability to bind to stress proteins or MHC molecules (see *e.g.*, Li at col. 46, lines 22-29, col. 42, line 63 to col. 43 line 3, and col. 44, lines 43-50). Thus, the pool of protease digested peptides used for complexing in claim 2 is not identical to the preselected antigen or hsp-eluted or MHC-eluted peptides used for complexing according to Li.

The teaching in Li of a method utilizing protease digestion is one in which the protease is combined with both the α2M and peptide in the complexing step (see *e.g.*, Li at col. 48, lines 32-44). Thus, according to Li, both the peptides and the α2M are mixed together in the presence of the protease so that the peptides become bound to the α2M during "activation" of α2M by the protease. This is different from the method of claim 2, in which protease digestion is used to treat the protein preparation *prior to the complexing step* in order to produce a population of peptides for complexing. Li does not teach such a step of digesting a protein preparation to produce a population of peptides which is then used for complexing with α2M. The complexes made according to claim 2 are thus expected to comprise a substantially different population of peptides than those made according to the method of Li, because the protease digestion produces peptides that are not naturally occurring within the cell and therefore can not be present for complexing according to the method of Li.

With respect to the Examiner's statement regarding the teaching in Li at col. 12, lines 24-27, Applicant respectfully submits that this teaching in Li does not relate to *in vitro* made complexes and is instead an example of unpurified endogenous complexes, *i.e.*, an α2M preparation which includes crude cell lysate comprising α2M (see page 12, para. 1 of the

Office Action). Such endogenous complexes do not anticipate the complexes of claim 2, which are made *in vitro*, because the *in vitro* made complexes would be expected to comprise different peptides in different amounts than complexes purified from a cell, for the reasons discussed above, including the protease digestion specified by claim 2.

In view of the above, Applicant submits that Li fails to anticipate claim 2 or its dependent claims, 17, 19, 20, 23, 25-32, and 35, and respectfully requests that the Examiner's rejection under 35 U.S.C. § 102(e) be withdrawn.

4. The Rejection Under 35 U.S.C. § 103(a) Should Be Withdrawn

The Examiner rejected claims 1-3, 15, 17, 19, 20, 23, 25-33, and 35 under 35 U.S.C. § 103(a) as allegedly unpatentable over WO 02/11669 ("Armen") in view of U.S. Patent No. 6,168,793 ("Srivastava"). In response, Applicant notes that the rejection is moot as it applies to claims 1 and 3, which have been canceled herein. With respect to claim 2, Applicant respectfully submits that claim 2, and its dependent claims, are patentable over Armen in view of Srivastava for the reasons set forth below.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim: (1) the cited references, when combined, teach or suggest every element of the claim; (2) there is some suggestion or motivation to modify the reference or combine the reference teachings to arrive at the claimed invention; and (3) there must have been a reasonable expectation of success for making the claimed combination in the art at the time of filing. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Applicant submits that the Examiner has failed to establish a *prima facie* case of obviousness because Armen, when combined with Srivastava, does not teach or suggest every element of independent claim 2. Claim 2 recites a method for treating cancer by administering a composition comprising a population of complexes of α2M and antigenic peptides which are made *in vitro*. The claim further specifies that the population of complexes was produced by a method comprising digesting a protein preparation comprising at least 50 different proteins present in cells of said type of cancer with one or more proteases to produce a population of antigenic peptides, and complexing the population of antigenic peptides to alpha-2-macroglobulin *in vitro*.

The Examiner acknowledges that Armen does not teach or suggest a composition comprising a population of complexes according to claim 2 (see p. 14, para. 2 of the Office Action). Applicant further notes that Armen does not teach or suggest the *in vitro* made complexes according to claim 2. Instead, Armen teaches that for *in vitro* complexing, a *selected* antigen is used on the basis of its known immunogenicity (see *e.g.*, Armen at p. 32, lines 28-32, and p. 33 lines 22-24) or pools of peptides are used that are *selected* on the basis of their binding to either heat shock proteins, α2M molecules or MHC molecules (see *e.g.*, Armen at p. 30, lines 23-34). Thus, according to the methods of Armen, peptides or proteins are *selected* for complexing with α2M, either based on known immunogenicity (in the case of known antigens) or based on predicted immunogenicity (in the case of binding to heat shock proteins, α2M molecules or MHC molecules).

The complexes taught by Armen are different from the complexes made according to claim 2 because the complexes of Armen are either (1) endogenously (not *in vitro*) complexed, *i.e.*, the α2M and antigenic peptides are isolated already complexed with each other (see *e.g.*, Armen at Sec. 4.2.1, p. 20-22); or (2) complexed *in vitro* but without the protease digestion specified in claim 2 (see *e.g.*, Armen at Sec. 4.2.1.1, p. 22-24). Both the endogenous and the *in vitro* made complexes produced according to Armen are different from the complexes produced according to claim 2 for the reasons discussed above in relation to Li. As in Li, Armen uses a protease step for formation of the complexes (see e.g., Armen at p. 22 line 34 to p. 23 line 33), and not to produce a population of antigenic peptides for complexing according to claim 2. Moreover, there is no motivation in Armen to use protease digestion to produce a population of peptides according to the method of claim 2 because, according to Armen, peptides (or proteins) are selected for complexing based on their antigenicity or immunogenicity (*i.e.*, either they are known antigens or potential antigens based on their binding to stress proteins or MHC molecules, see *e.g.*, Armen at p. 30 lines 32-34 and p. 32 lines 28-32). Since the use of protease digestion according to claim 2 could destroy the antigenic determinants of such peptides (or proteins) selected for their known antigenicity, there would be no motivation to include such a step in the method of Armen. Nor is it apparent, and the Examiner has not explained, how the use of protease for complexing of α2M to peptide as taught by Armen renders obvious the use of protease prior to the complexing step to produce a population of peptides according to claim 2. This deficiency of Armen is not remedied by Srivastava, which does not teach *in vitro*

complexing, much less the use of proteases to produce peptides for such *in vitro* complexing methods.

The specific teaching in Armen regarding compositions comprising more than one antigenic molecule specifies at most three antigenic molecules in the composition (see Armen at p. 13, lines 10-14), which in no way suggests the complexes of the claims which are made by produced by a method comprising digesting a protein preparation comprising at least 50 different proteins present in cells of said type of cancer with one or more proteases to produce a population of antigenic peptides, and complexing the population of antigenic peptides to alpha-2-macroglobulin *in vitro*.

The Examiner relies on Srivastava for the teaching of a population of complexes that is admittedly missing from Armen (see the Office Action at p. 14, para. 2). However, Srivastava teaches no more than the isolation of endogenous heat shock protein-peptide complexes from cells. Srivastava does not teach or suggest complexes such as those made *in vitro* according to the method of claim 2. The differences between complexes made *in vitro* according to the claims and endogenous complexes isolated from cells are described above. Moreover, it is not apparent, and the Examiner has not explained, how such complexes isolated from cells would render obvious the presently claimed *in vitro* made complexes.

In view of the above, Applicant submits that Armen, combined with Srivastava, fails to render obvious claim 2, or its dependent claims, 17, 19, 20, 23, 25-32, and 35, and respectfully requests that this rejection be withdrawn.

5. The Obviousness-Type Double Patenting Rejections Should Be Withdrawn

The legal standard for an obviousness-type double patenting rejection requires a comparison of what is claimed in the earlier patent, not what was disclosed in the specification of the earlier patent. See *e.g.*, *General Foods, Inc. v. Studiengesellschaft Köhle mbH*, 972 F.2d 1272, 1280-81 (Fed. Cir. 1992). Although the specification may be used to determine the meaning of terms used in the claims, the specification may not be used as prior art. See *e.g.*, *In re Vogel*, 422 F.2d 438 (C.C.P.A. 1970).

The Rejection over U.S. Patent No. 6,984,389

The Examiner rejected claims 1-3, 17, 19, 20, 23, 25-33, and 35 over claims 48-50 of Li, U.S. Patent No. 6,984,389 ("the '389 patent") in view of the teachings of WO 02/11669 ("Armen") under the judicially created doctrine of obviousness-type double patenting. In response, Applicant notes that the rejection is moot as it applies to claims 1 and 3, which have been canceled herein. With respect to claim 2, Applicant respectfully submits that claim 2 is not obvious over claims 48-50 of the '389 patent.

Claim 48 of the '389 patent recites a method for treating cancer that comprises administering a "purified alpha-2-macroglobulin preparation." Claim 49 of the '389 patent recites a method that comprises administering "a purified alpha-2-macroglobulin preparation comprising a population of non-covalent alpha-2-macroglobulin-peptide complexes obtained from cancerous tissue of the subject." Claim 50 of the '389 patent recites a method that comprises administering a suboptimal amount of a purified alpha-2-macroglobulin preparation comprising a population of complexes that (i) display the antigenicity of a tumor-specific antigen or tumor-associated antigen or (ii) are isolated from cancerous tissue of the subject to be treated.

Claim 2 is not rendered obvious by claims 48-50 of the '389 patent because the claims of the '389 patent do not teach or suggest the *in vitro* made complexes according to claim 2, in which a protein preparation is digested with one or more proteases to produce the antigenic peptides used in the *in vitro* complexing step. Claim 49 of the '389 patent recites complexes "obtained from cancerous tissue of the subject." Thus, claim 49 does not suggest *in vitro* made complexes and is instead directed to endogenous complexes. Such endogenous complexes differ from the *in vitro* made complexes of claim 2 because the *in vitro* made complexes would be expected to comprise different peptides in different amounts than complexes purified from tissue, for the reasons set forth above in the response to the rejections under 35 U.S.C. §§ 102(e) and 103(a), including, *inter alia*, the protease digestion used to produce the peptides used for complexing. It is not clear, and the Examiner has not explained, how endogenous complexes obtained from tissue render obvious the *in vitro* made complexes of claim 2.

Claims 48 and 50 do not state or suggest that the "purified alpha-2-macroglobulin preparation" is made *in vitro*. Claim 50, in an alternative, specifies that the complexes are

isolated from cancerous tissue, and thus are endogenous complexes that do not suggest the *in vitro* made complexes of the presently claimed invention for the reasons discussed above. To the extent that the specification of the '389 patent informs the meaning of the claim term "purified alpha-2-macroglobulin preparation" it fails to suggest the *in vitro* made complexes of the instant claims for all of the reasons discussed above. Specifically, the '389 patent does not teach or suggest a purified alpha-2-macroglobulin preparation that is *in vitro* made complexes in which a protein preparation is digested with one or more proteases to produce the antigenic peptides used in the *in vitro* complexing step.

With respect to claim 2 in particular, the Examiner acknowledged that claims 48-50 of the '389 patent do not teach a population of complexes produced by exposing a protein preparation to protease (see the Office Action at p. 17). The Examiner relies on Armen for this teaching. However, as discussed above in response to the rejection under 35 U.S.C. § 103(a), Armen does not teach or suggest the protease digestion specified in claim 2. Thus, claims 48-50 of the '389 patent, in view of Armen, do not render obvious the method of claim 2.

In view of the above, Applicant submits that claims 48-50 of the '389 patent do not render obvious pending claim 2, or its dependent claims, 17, 19, 20, 23, 25-32, and 35, and respectfully request that the Examiner withdraw this rejection.

The Provisional Rejection Over U.S. Patent Application No. 10/546,106

The Examiner also provisionally rejected claims 1-3, 19, 20, 23, 25, 32, 33, and 35 over claims 2-4 and 8 of copending U.S. Patent Application No. 10/546,106 ("the '106 application") in view of the teachings of Armen under the judicially created doctrine of obviousness-type double patenting. In response, Applicant notes that claims 1 and 3 have been canceled herein, rendering the rejection moot as it applies to those claims. With respect to claim 2, Applicant respectfully submits that claim 2 is not rendered obvious by claims 2-4 and 8 of the '106 application.

Claims 2-4 and 8 of the '106 application are directed to a method of treating cancer comprising administering a complex of alpha (2) macroglobulin and antigenic molecule, wherein the complex was *isolated from a bodily fluid* of a mammal having cancer. These claims do not teach or suggest a composition comprising a population of complexes made *in*

vitro according the method of pending claim 2. The differences between endogenous complexes isolated from a bodily fluid and complexes made *in vitro* according to claim 2 are evident. For example, the peptides comprising the complexes isolated from a bodily fluid will be substantially different from the proteins and peptides comprising the complexes made according to claim 2, which are derived from cancer cells. It seems clear that the α2M complexes isolated from a bodily fluid, presumably comprising proteins or peptides present in the bodily fluid, would not be expected to be the same as or to suggest the *in vitro* made complexes of claim 2, which are made from a multiplicity of peptides of cancer cells prepared by protease digestion of a protein preparation. Thus, the complexes recited in claims 2-4 and 8 of the '106 application are substantially different from and do not suggest the complexes recited in the pending claims. Armen does not rectify these deficiencies of the claims of the '106 application, as discussed above.

In view of the above, Applicant respectfully submits that claims 2-4 and 8 of the '106 application do not render obvious pending claims 2, 19, 20, 23, 25, 32, and 35, and respectfully request that the Examiner withdraw this rejection.

CONCLUSION

Applicant believes that the present claims meet all of the requirements for patentability. Entry and consideration of the foregoing amendments and remarks into the file of the subject application are respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicant's undersigned attorney invites the Examiner to telephone her at the number provided below.

Respectfully submitted,

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